Should we test for *Helicobacter pylori* before treating gastroesophageal reflux disease?

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P Moayyedi. Should we test for *Helicobacter pylori* before treating gastroesophageal reflux disease? Can J Gastroenterol 2005;19(7):425-427.

Gastroesophageal reflux disease (GERD) is a common problem in childhood. The cause is uncertain but because the incidence of GERD is increasing in developed countries and the prevalence of *Helicobacter pylori* is decreasing, it has been suggested that this infection protects against GERD. Observational data from 95 children, however, suggest that *H pylori* eradication does not have a deleterious effect on GERD and this is supported by randomized controlled trials in adults. *H pylori* eradication may also reduce the efficacy of proton pump inhibitor therapy in infected patients. There are no data from children but inferences from randomized controlled trials in adults suggest this effect is likely to be modest and of uncertain clinical significance.

H pylori is an important risk factor for distal gastric adenocarcinoma. It is likely that treating the infection in childhood will prevent pre-malignant changes associated with *H pylori* from developing in the future. A meta-analysis of four randomized controlled trials suggest that there is a statistically significant impact on healing of chronic gastritis after one year compared with placebo (RR of chronic gastritis: 0.27; 95% CI 0.23 to 0.32). *H pylori* eradication is therefore recommended in children with GERD that are having an endoscopy. However, when the diagnosis of GERD is being made clinically or by pH monitoring, it is not necessary to screen for *H pylori*.

Key Words: Esophagitis; Gastroesophageal reflux disease; *H pylori* eradication; *Helicobacter pylori*; Proton pump inhibitor therapy

Gastroesophageal reflux disease (GERD) is a common disorder of early infancy and symptoms occur in 6% to 8% of children aged 10 to 19 years (1). The pathophysiology of GERD is likely to be similar to adults, with transient relaxation of the lower esophageal sphincter being an important factor (2); however, asymptomatic episodes of acid reflux are more common in children (3). The incidence of GERD is rising in developed countries and it has been postulated that this could be due to the falling prevalence of *Helicobacter pylori* (4). There are also reports that *H pylori* eradication reduces the efficacy of proton pump inhibitor (PPI) therapy (5). In addition, *H pylori* infection is associated with gastric adenocarcinoma and this may be potentiated in GERD patients on long-term acid suppression (6). The present article will assume that *H pylori*-status testing is performed with the intention to treat the infection. The evidence for *H pylori* eradication in GERD patients will be reviewed; specifically, in terms of exacerbating

Devrait-on procéder au dépistage du *Helicobacter pylori* avant de traiter le reflux gastro-œsophagien pathologique?

Le reflux gastro-œsophagien pathologique (RGOP) est un trouble courant pendant l'enfance. Sa cause demeure incertaine, mais puisque l'incidence de RGOP augmente dans les pays industrialisés tandis que la prévalence du *Helicobacter pylori* diminue, on postule que cette infection protège contre le RGOP. Cependant, des données d'observation auprès de 95 enfants laissent supposer que l'éradication du *H pylori* n'a pas d'effet délétère sur le RGOP, ce qui est étayé par des essais aléatoires et contrôlés chez les adultes. L'éradication du *H pylori* pourrait également réduire l'efficacité d'un traitement aux inhibiteurs de la pompe à protons chez les patients infectés. Aucune donnée ne porte sur les enfants, mais d'après les inférences d'essais aléatoires et contrôlés chez les adultes, cet effet est probablement modeste et d'importance clinique incertaine.

Le *H pylori* est un facteur de risque important d'adénocarcinome gastrique distal. Il est probable que le traitement de l'infection pendant l'enfance évitera que l'apparition des modifications pré-malignes associées au *H pylori* plus tard. Une méta-analyse de quatre essais aléatoires et contrôlés indique la présence de répercussions statistiquement significatives de la guérison de la gastrite chronique au bout d'un an par rapport à un placebo (RR de gastrite chronique : 0,27; 95 % IC 0,23 à 0,32). Par conséquent, l'éradication du *H pylori* est recommandée chez les enfants atteints de RGOP qui subissent une endoscopie. Cependant, lorsque le diagnostic de RGOP s'effectue en clinique ou au moyen d'une pH-métrie, il n'est pas nécessaire de procéder au dépistage du *H pylori*.

symptoms, reducing the efficacy of PPI therapy and reducing long-term complications.

THE INFLUENCE OF *H PYLORI* ERADICATION ON GERD

In a systematic review of 20 studies, *H pylori* infection was less prevalent in patients with GERD compared with controls (7). This was particularly evident in Far East Asian studies. The association between *H pylori* and GERD could be due to confounding or bias because the systematic review was based on observational data (8) and relates to all subjects, not only those that already have reflux disease.

An observational study of 95 children (9) suggested that eradication therapy did not have an impact on GERD, with reflux symptoms being similar among *H pylori*-negative subjects and both successful and failed eradication groups (after a mean follow-up of almost one year [9]); this was additionally

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Figure 1) Randomized controlled trials reporting the efficacy of *Helicobacter pylori* eradication versus placebo antibiotics in chronic corpus gastritis. The outcome is a relative risk of moderate to severe gastritis versus none or mild gastritis after one year. Data from references 22, 23, 25 and 26

supported by another study (10) in 90 children. There are, however, limited data in children because the prevalence of *H pylori* infection is low and no randomized controlled trials exist; therefore, inferences about the effects of *H pylori* eradication in GERD need to be drawn from studies on adult patients. There are two randomized controlled trials (11,12) of *H pylori* eradication on relapse in adult GERD patients after treatment withdrawal. One trial (11) suggested that *H pylori* reduced GERD symptoms and the other (12) reported no significant impact from *H pylori* eradication. Overall, *H pylori* eradication is unlikely to have a major impact on the relapse of reflux symptoms in untreated patients.

THE IMPACT OF *H PYLORI* ERADICATION ON PPI EFFICACY

One study (13) reported that H_2 -receptor antagonist therapy had similar effectiveness in both *H pylori*-positive and -negative children with histological esophagitis; however, only 15 of 109 children were infected. PPI therapy has been shown to be the most effective pharmacological therapy for GERD in children (14); however, the impact of *H pylori* on PPI efficacy has not been studied in children so inferences must be made from adult data. Studies (15) have suggested that antisecretory therapy causes greater acid suppression in *H pylori*-infected individuals; furthermore, *H pylori* eradication impairs the ability of PPI therapy to reduce acid output (16). While the area under the curve for intragastric pH may be significantly different in patients after *H pylori* eradication, it is unclear whether this has any clinical implications. A large study (17) in 971 patients (40% *H pylori*-positive) reported that the healing of esophagitis was significantly more effective in *H pylori*-positive patients; however, there is doubt about the clinical significance of this finding because there was less than a 5% difference between the two groups at eight weeks. That study (17) was supported by two randomized controlled trials (18,19) that reported a trend for reduced healing of esophagitis in patients given *H pylori* eradication therapy.

GERD is a chronic disease and patients often need long-term therapy. The impact of *H pylori* eradication on maintenance therapy also needs evaluation. Two randomized trials (12,19) have assessed this and there was no difference in relapse rate between those receiving active and placebo antibiotics. A United Kingdom trial (12) reported an 83% relapse rate in both groups, while a Hong Kong study (19) found that relapse occurred in 10 of 53 patients assigned to eradication therapy and eight of 51 patients given placebo antibiotics. Once the acute healing and maintenance therapy were combined in the Hong Kong trial (19), the probability of treatment failure was significantly higher in the eradication group (43%) compared with the *H pylori*-positive group (21%).

Rebound acid secretion occurs in patients given *H pylori* eradication therapy on discontinuation of PPI therapy that persists for at least 56 days (20). This does not seem to have a major clinical impact, however, because relapse of GERD after stopping PPI therapy was similar in those randomly assigned to eradication therapy or placebo (12).

THE EFFECT OF *H PYLORI* ERADICATION ON LONG-TERM COMPLICATIONS OF THE INFECTION

Children with GERD that are infected with *H pylori* will be placed on PPI therapy. Acid suppression will change the topography of infection from an antral- to a corpus-predominant disease (21). This, in turn, may lead to an increased risk of gastric atrophy and intestinal metaplasia (6,22), although data are conflicting (23). What is certain, is that *H pylori* is a major risk factor for noncardia gastric adenocarcinoma (24), and children with this infection have at least a fivefold increased risk of developing stomach neoplasia in later life. This risk is likely to be reversed with *H pylori* eradication. There is controversy as to when the premalignant changes induced by *H pylori* become irreversible, but in children it is very likely that eradication therapy will prevent most gastric adenocarcinoma in later life. A literature search identified four randomized controlled trials (22,23,25,26) with extractable data that show that anti-*H pylori* therapy usually returns the mucosa to normal, or with just mild inflammation, after one year (Figure 1). Although this is unlikely to benefit children immediately, in the long term their risk of complicated and uncomplicated peptic ulcer disease (27) and distal gastric cancer (28) will be reduced.

CONCLUSIONS

It is possible that *H pylori* may cause hypochlorhydria in some cases and this will protect against GERD if the lower esophageal sphincter is weak. This is relatively rare in Western countries, but is more common in Far East Asia and, of note, the two trials (18,19) that reported a possible deleterious effect of *H pylori* eradication on esophagitis were from Hong Kong. *H pylori*-induced hypochlorhydria is likely very rare in children and, therefore, eradication is unlikely to have an important impact on PPI efficacy or GERD.

When the diagnosis of GERD is being made on clinical grounds or through pH studies, there is no need to test for *H pylori* infection. If an endoscopy is being performed it seems sensible to test for *H pylori* and offer eradication therapy if the patient is positive. This may prevent some children from developing peptic ulcer disease and gastric cancer as adults.

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